REMARKS

Claims 8, 10-11 and 15 stand rejected under 35 U.S.C. §112, second paragraph for purportedly being indefinite. In view of the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection of the claims.

Regarding claim 8, the Examiner states that there is insufficient antecedent basis for the limitation "in step c)." In view of the amendment of claim 8 Applicants request that the Examiner reconsider and withdraw the rejection.

Claim 8 depends on claim 7, which depends on claim 1 and therefore incorporates all the limitations of claim 1. Claim 1 recites a "step c)" and therefore provides the antecedent basis for the term "in step c)" recited in claim 8. As, such, Applicants request that the rejection as it is applied to claim 8 be withdrawn.

Regarding claims 10, the Examiner states that the limitations "the partial libraries in the compartments" in claim 7 and "the amplification of the partial libraries" in claim 1 lack antecedent basis. Applicants disagree. Claim 10 depends on claim 1 and therefore incorporate all the limitations of claim 1. Claim 1 states that the variant library is divided into "a number of compartments (W_0), ...where each compartment contains a partial library." Therefore claim 1 discloses "partial libraries" and provides the necessary antecedent basis for the term "partial libraries" in claim 10. In view of the foregoing remarks, Applicants request that the rejection as it is applied to claim 10 be withdrawn.

Regarding claim 11, Applicants have amended claim 11 to depend on claim 6 which recites "...wherein in step c) also an amplification of the partial library takes place..." and therefore provides the necessary antecedent basis for claim

11. Support for this amendment is found in original claim 11 that depended on any one of claims 1-6. In view of the amendment to claim Applicants request that the rejection as it is applied to claim 11 be withdrawn.

Regarding claim 15, the Examiner states that the limitation "the test for a biocatalytic activity" in claim 1 lacks antecedent basis. Applicants have amended claim 15 to depend on claim 2, which recites "the wanted property is a biocatalytic activity" and therefore provides the necessary antecedent basis for the term "biocatalytic activity" recited in claim 15. Support for this amendment is found in original claim 15 that depended on any one of claims 1-14. In view of the amendment to claim 15, Applicants request that the rejection as it is applied to claim 15 be withdrawn.

Claims 1-5, 7, 9, 12 and 14 stand rejected under 35 U.S.C. §102(b) for purportedly being anticipated by Hubner et al. Applicants disagree and in view of the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection.

Hubner et al. relate to modifications of ribonuclease T1 specificity and disclose an assay for the screening of a single clone (cf. Hubner et al., abstract; p. 1372, right column) for a desired phenotype.

The aim of plating microorganisms, as disclosed in Hubner et al., is to initially separate a single clone from all the other variants and to test the single clone for a specified property (phenotype). By this method each variant clone with its associated single phenotype and related genotype is separated from each of the other variants. Thus, a single variant can be separated from the rest of the variants in a single step. All further steps, including testing of the phenotype, are then carried out separately on each variant so that all the test results obtained can be unambiguously linked to the single genotype of each variant. Therefore, after plating, every phenotype can be assigned to its corresponding genotype at all times (see Hubner et al., p.1372, right column).

In contrast, in Applicants' method step b), the variants are divided into compartments that, unlike Hubner et al., intentionally comprise multiple variants, B_0/W_0. Those compartments are then assayed in step c) for a particular phenotype. If a phenotype is detected in one of those compartments, one of skill in the art cannot assign that detected phenotype to a particular genotype because that compartment comprises multiple variants: the genotype and phenotype in step c) are therefore "uncoupled." Hubner et al. do not disclose the method according to claim 1, wherein genotype and phenotype are "uncoupled."

In step d) of the claimed method the compartment having the detected phenotype is then selected and in step e) the variants further divided into more compartments each compartment having a number of variants. Then the new compartments are assayed for the desired phenotype, step c). Steps c) through e) are repeated until the compartments contain, at a maximum, one variant. Once the compartments contain maximally one variant, and the desired phenotype is detected in a compartment, the detected phenotype can be assigned to the genotype of the variant in that compartment.

Therefore, by the claimed method, (1) the number of genotypes correlated or contributing to a detected phenotype decreases every time steps c) to e) are repeated, and (2) the original variant library is divided into partial libraries which get smaller every time steps c) through e) are repeated.

At the end of the claimed iterative method, a complete separation between all the variants is achieved and the phenotype and genotype coupling is restored. Hubner et al. does not teach a method comprising the steps recited in the claimed method and do not teach a method that comprises uncoupling the phenotype and genotype of the variants.

The foregoing demonstrates that Hubner et al. does not teach each and every limitation of Applicants' method and therefore does not anticipate the invention as claimed. Applicants request that the Examiner reconsider and

withdraw the rejection of claims 1-5, 7, 9, 12 and 14 under 35 U.S.C. §102(b) in view of Hubner et al.

Claims 6, 8, 11 and 13 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Hubner et al. as applied to claims 1 and 7 in combination with Selifonov. Applicants disagree and in view of the following remarks request that the Examiner reconsider and withdraw the rejection.

As discussed above, Hubner et al. relate to modifications of ribonuclease T1 specificity and disclose an assay for the screening of a single clone. Thus, Hubner et al. do not disclose a method according to claim 1 comprising steps wherein a library of variants are divided into compartments such that the compartments comprise a partial library and then assaying the phenotype of those compartments. Hubner et al. does not teach a method such as Applicants where the genotype and phenotype are "uncoupled", in that one of skill in the art could not link the phenotype observed for a particular compartment with a particular genotype contained within that compartment.

The method described by Hubner et al. does not teach or suggest uncoupling genotypes and phenotypes, or that the phenotype and genotype should be uncoupled, or how such uncoupling can be achieved.

Selifonov et al. do not compensate for Hubner et al.'s deficiencies because Selifonov et al. also disclose plating transformed *E. coli*, which have been obtained through DNA shuffling, to obtain single clones that are then assayed for a desired phenotype. See e.g., page 95, line 15 "In one aspect, library members, e.g., cells, viral plaques, spores or the like are separated on solid media to produce *individual* colonies (or plaques)"(emphasis added). As discussed above, microorganisms are plated to separate the variant clones away from each other so that every grown colony can be referred back to a single clone. Moreover, because the single clones are separated, Selifonov et al. assay the phenotype of each clone individually so that the detected phenotype is associated

with the genotype of a particular clone. Accordingly, in Selifonov et al. the phenotype can be referred back to the single clone at any time.

In contrast, in the claimed method the phenotype is assayed for a mixture of variants and the detected phenotype can not be associated with a particular genotype because the detected phenotype is the product of all the clones of the compartment, i.e. from the sum of all single phenotypes of these clones. The number of clones in a subsequent compartments decreases every time steps c) to e) are repeated until a single clone remains. It is only after steps c) through e) have been repeated enough times such that a compartment has, maximally, only one variant that the detected phenotype is once again coupled to a particular genotype.

Selifonov et al. in combination with Hubner et al. does not teach or suggest a method wherein the phenotype and genotype are uncoupled, nor does their combination provide any teaching or suggestion that the phenotype and genotype should be uncoupled, or how an uncoupling of genotype and phenotype can be achieved. As such, Hubner et al. in combination with Selifonov et al. fail to teach or suggest the invention as claimed and as such does not render the claimed invention obvious.

In view of the foregoing remarks, Applicants request that the Examiner reconsider and withdraw the rejection of claims 6, 8, 11 and 13 under 35 U.S.C. 103(a) over Hubner et al. in combination with Selifonov.

Claim 10 stands rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Hubner et al. in combination with Nepolitano. Applicants disagree.

The deficiencies of Hubner et al. are discussed above, in particular, Hubner et al. fails to teach or suggest a method wherein the phenotype of compartments comprising a partial library of multiple variants is assayed: in which case the phenotype can not be associated with a particular genotype of the

variants in the compartment, i.e., the phenotype and genotype are uncoupled. Nepolitano fails to compensate for Hubner et al.'s deficiencies.

Like Hubner et al., Nepolitano et al. relate to the complete amino acid sequence and in vitro expression of Rat NF-M. Nepolitano does not teach or suggest a method wherein phenotype and genotype are uncoupled. Nor do they teach or suggest that the phenotype and genotype should be uncoupled or how such uncoupling would be achieved. Thus the combination of Hubner et al. and Nepolitano et al. fails to render the invention as claimed obvious.

In view of the foregoing remarks, Applicants request that the Examiner reconsider and withdraw the rejection of claim 10 under 35 U.S.C. 103(a) over Hubner et al. in combination with Nepolitano.

Claim 15 stands rejected under 35 U.S.C. 103(a) for purportedly being unpatentatble over Hubner et al. in view of Korn et al. Applicants disagree.

The deficiencies of Hubner et al. are discussed above, in particular, Hubner et al. fails to teach or suggest a method wherein the phenotype of compartments comprising a partial library, and therefore multiple variants, is assayed, in which case the detected phenotype can not be associated with a particular genotype of the variants in the compartment, i.e., the phenotype and genotype are uncoupled. Korn et al. fails to compensate for Hubner et al.'s deficiencies.

Korn et al. relate to ribonuclease assays utilizing toluidine blue indicator plates. Korn et al., like Hubner et al., do not teach or suggest a method wherein phenotype and genotype are uncoupled, or that phenotype and genotype should be uncoupled, or how such uncoupling would be achieved.

Thus the combination of Hubner et al. and Korn et al. fail to render the invention as claimed obvious.

In view of the foregoing remarks, Applicants request that the Examiner reconsider and withdraw the rejection of claims 6, 8, 11 and 13 under 35 U.S.C. 103(a) over Hubner et al. in combination with Korn et al.

As discussed in Applicants' specification, the claimed method provides for analyzing up to a million or more variants with one test and simultaneously for a wanted property. Therefore, the time needed for the screening of the library and the costs needed to test for the wanted property are reduced by a corresponding factor. Variants, which possess the wanted properties, can by isolated from the original variant mixture in a secure and reproducible way (see page 3, line 26 to page 4, line 2).

Applicants also disclose in their specification that an important advantage of the present invention in comparison to conventional methods, which contain mutagenesis and selection steps, is that in the claimed method one starts from a large library that *a priori* contains the variant with the wanted properties. That means that after the screening, one of skill in the art does not obtain a suboptimal variant, which needs to be further improved through additional cycles of mutation and recombination (page 5, lines 25-29).

In the method according to the present invention genotype and phenotype are uncoupled, the clone responsible for the wanted property, which for instance comprises a desired enzymatic activity, can be retrieved and isolated from the mixture of clones with the method according to the present invention. One of skill in the art would find it surprising and unexpected that it is possible to retrieve the clone responsible for the wanted property from the mixture of clones with a screening method in which genotype and phenotype are uncoupled because as all known screening methods are based on the coupling of phenotype with a particular genotype. Therefore, the claimed invention is both novel and non-obvious over the prior art .

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket # 102520.57766US).

Respectfully submitted,

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